IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2663
Steven M. RUBEN	Art Unit: 1644
Appl. No.: 10/662,429	Examiner: HUYNH, PHUONG N.
Filed: September 16, 2003	Atty. Docket: 1488.1890003/EJH/SAC
For: **Apoptosis Inducing Molecule I**	

REQUEST FOR INTERFERENCE WITH A PATENT PURSUANT TO 37 C.F.R § 41.202(a)

Commissioner for Patents
PO Box 1450
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Sir:

Pursuant to 37 C.F.R. § 41.202(a), Applicant hereby requests that an interference be declared on the subject matter of RUBEN PROPOSED COUNT A (attached as Appendix A) between the above-captioned application and claims 1-26, 30-37, 39-43, and 45-59 of U.S. Patent No. 6,284,236 issued September 4, 2001 to Wiley *et al.* (Appendix B). Concurrently herewith, Applicant is filing in this application a *Prima Facie* Showing of Entitlement to Judgment Under 37 C.F.R. § 41.202(d) and Showing of Compliance With 35 U.S.C. § 135(b), which demonstrates *prima facie* entitlement to judgment based on priority of invention under 35 U.S.C. § 102(g) relative to the patentee and that the requirements of 35 U.S.C. § 135 have been met.

I. BACKGROUND

Ruben's captioned Application No. 10/662,429 ("the '429 application") filed September 16, 2003 is a divisional of Application No. 08/816,981, filed March 13, 1997 which claims the benefit under 35 U.S.C. § 119(e) of provisional Application No. 60/013,405 filed March 14, 1996 ("the '405 application").

Wiley *et al.* ("Wiley") Patent No. 6,284,236 ("the '236 patent") issued from Application No. 09/320,424, filed May 26, 1999, which is a continuation-in-part of Application No. 09/190,046, filed November 10, 1998, now abandoned, which is a continuation-in-part of Application No. 09/048,641, filed March 26, 1998, now abandoned, which is a continuation-in-part of Application No. 08/670,354, filed June 25, 1996, now U.S. Patent No. 5,763,223, which is a continuation-in-part of Application No. 08/548,368, filed November 1, 1995, now abandoned, which is a continuation-in-part of Application No. 08/496,632, filed June 29, 1995, now abandoned ("the '632 application").

II. REQUEST FOR INTERFERENCE WITH A PATENT

A. 37 C.F.R. § 41.202(a)(1)

Under the provisions of 37 C.F.R. § 41.202(a)(1), Applicant seeks to have an interference declared between pending claims 8-10, 12-15, 17, 25, 27, and 30-38 of the captioned application and claims 1-26, 30-37, 39-43, and 45-59 of unexpired Wiley Patent No. 6,284,236 issued September 4, 2001 (Appendix B).

B. 37 C.F.R. § 41.202(a)(2)

Applicant proposes RUBEN PROPOSED COUNT A (Appendix A). RUBEN PROPOSED COUNT A recites:

An isolated polypeptide comprising amino acids 1 to 281 of SEQ ID NO:2 or a fragment thereof, wherein said fragment has apoptosis inducing activity.

Claims of a patent or an application are presumed to correspond to a count if "the subject matter of the count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of the claim. 37 C.F.R. § 41.207(b)(2).

1. Wiley Claims Which Correspond to Ruben Proposed Count A

Applicant proposes that claims 1-26, 30-37, 39-43, and 45-59 of the Wiley '236 patent should be designated as corresponding to RUBEN PROPOSED COUNT A. Claims 1-26, 30-37, 39-43, and 45-59 are drawn to the full-length TRAIL protein, the TRAIL extracellular domain fragment, variants of the extracellular domain containing conservative amino acid substitutions, fusion proteins comprising TRAIL or a fragment thereof, TRAIL polypeptides expressed in bacteria, oligomers of two or more TRAIL polypeptides or fragments, and compositions comprising TRAIL, TRAIL fragments, TRAIL oligomers, TRAIL variants, or fragments thereof. Amino acids 1 to 281 of SEQ ID NO:2 recited in the '236 patent claims are 100% identical to amino acids 1 to 281 of SEQ ID NO:2 of the captioned application. For clarity, the Wiley sequence of the '236 patent will be referred to as "SEQ ID NO:2 ('236)," and the Ruben sequence of the captioned application will be referred to as "SEQ ID NO:2 ('429)." These polypeptides are referred to as AIM-I by Ruben and TRAIL by Wiley. Claims 27-29, 38, and 44 are believed to recite subject matter which does not correspond to the count.

Claim 1 of the '236 patent recites a TRAIL polypeptide at least 90% identical to SEQ ID NO:2 ('236). Claim 1 is anticipated by Ruben Proposed Count A because Ruben Proposed Count A recites a polypeptide comprising an amino acid sequence that is at least 90% identical to amino acids 1 to 281 of SEQ ID NO:2 ('236). Claim 2 is anticipated because amino acids 1 to 281 of SEQ ID NO:2, as recited in Ruben Proposed Count A, is identical to amino acids 1 to 281 of SEQ ID NO:2 of the claim. Claim 3 is anticipated by Ruben Proposed Count A because Ruben Proposed Count A recites a polypeptide comprising amino acids 1 to 281 of SEQ ID NO:2, and this polypeptide is encoded by the cDNA insert of the recombinant vector deposited in strain ATCC 69849. Even if minor sequencing differences

were present in the cDNA insert of the recombinant vector deposited in strain ATCC 69849, Rube Proposed Count A would still render Claim 3 obvious.

Claims 4-7, 9-10 and 33-36 are drawn to the TRAIL extracellular domain fragment and other TRAIL fragments with apoptotic activity. Ruben Proposed Count A anticipates or alternatively, renders obvious these claims. Ruben Proposed Count A anticipates these claims because Ruben Proposed Count A is encompassed by the claimed TRAIL fragments. Alternatively, these claims are rendered obvious by Ruben Proposed Count A because one of ordinary skill in the art would have easily been able to identify these fragments based on the known structure function relationship of the TNF ligand family, as described in Gruss and Dower, *Blood 85*:3378-3404 (1995) (see Appendix D), and would have been motivated to do so based on the known need for soluble ligands. Claim 8 relates to variants of the extracellular domain and extracellular domain fragments containing conservative amino acid substitutions. One of ordinary skill in the art would have been motivated to combine Ruben Proposed Count A with the well-known structure/function relationship in the family of TNF ligands (see Appendix D), to make functional fragments with conservative amino acid substitutions, since such variants are commonly known to occur (Pakula, AA and Sauer, RT, *Annual Review of Genetics 23*:289-310 (1989) (Appendix C)). Thus, one of ordinary skill in the art would have known where substitutions could be made without affecting the function of the protein, and would have had a reasonable expectation of success in doing so. Accordingly, claim 8 which recites functional fragments with conservative amino acid substitutions is obvious over the polypeptide and polypeptide fragment explicitly recited in Ruben Proposed Count A and, thus, constitutes the same patentable invention.

Claims 11-22 are drawn to fusion proteins comprising a TRAIL polypeptide fused to a leucine zipper domain. A variety of leucine zipper domains, as well as their role in oligomerization of proteins, was well known in the prior art. Landschulz *et al.*, *Science*

240:1759 (1988) (Appendix E); Rabindran *et al.*, *Science 259*:230 (1993); PCT Publication WO 94/10308, entitled "Method of Preparing Soluble Oligomeric Proteins," published May 11, 1994 (Appendix F) (The '236 patent itself contains admissions that leucine zipper domains and their role in the oligomerization was known in the art. '236 patent at col. 12, line 37 to col. 13, line 60 (citing references published between 1989 and 1994, i.e., well before the earliest '236 patent priority date of June 29, 1995)). Furthermore, since it was well known that TNF ligand family members are oligomeric (*see* Appendix G), the skilled artisan would have been motivated to engineer TRAIL polypeptides with the propensity to oligomerize. Accordingly, claims reciting fusion proteins comprising a TRAIL polypeptide fused to a leucine zipper domain are obvious over the full-length TRAIL polypeptide and polypeptide fragments explicitly recited in Ruben Proposed Count A and thus constitute the same patentable invention.

Claims 23-26, 32, 37, 39-43, and 45-48, drawn to oligomeric forms of the TRAIL polypeptide, are inherently anticipated or alternatively, rendered obvious by Ruben Proposed Count A. That TNF ligand family members are oligomeric, particularly trimeric, proteins *in vivo* was well known. Beutler *et al.*, *Science 264*:667-668 (April 1994) (Appendix G) and Engelmann *et al.*, *J. Biol. Chem. 265*:14497-14504 (1990) (Appendix H). Thus, the ordinarily skilled artisan would have been motivated to produce oligomeric forms of the fragments recited in Ruben Proposed Count A. Accordingly, claims reciting oligomeric forms of TRAIL are either inherently anticipated or are rendered obvious over the full-length TRAIL polypeptide and polypeptide fragments explicitly recited in Ruben Proposed Count A and thus constitute the same patentable invention.

Along with reciting a leucine zipper domain, '236 patent claims 16-22 recite that either a growth hormone leader sequence or CMV leader sequence is fused to the N-terminus of the TRAIL polypeptide. Leader sequences were well known to promote secretion of

polypeptides produced in a cell. Watson *et al.*, Recombinant DNA: A Short Course. 96-97 W.H. Freeman & Co. (1983) (Appendix I). Moreover, it is a basic principle of recombinant protein expression, developed well prior to the invention of the interfering subject matter, that secretion of a recombinantly produced protein into the cell culture medium greatly facilitates isolation of the recombinantly produced protein. Ausubel *et al.*, Current Protocols in Molecular Biology 16 (1994) (Appendix J).

Indeed, the prior art had described the specific recited growth hormone and CMV leader sequences fused to heterologous proteins to promote secretion of heterologous proteins. Pecceu *et al.*, *Gene 97*:253-258 (1991) (Appendix K). Thus, the recitation of these leader sequences is not a patentable distinction from Ruben Proposed Count A, and all of claims 16, 17, and 19 should be designated as corresponding thereto.

Claims 30 and 31 recite the TRAIL protein and fragments thereof that have been recombinantly produced in *E. coli* cells. Recombinant production of proteins in *E. coli* is elementary to biotechnology and in no way constitutes a patentable distinction. See Appendix I. Thus, claims 30 and 31 are either anticipated or rendered obvious by Ruben Proposed Count A.

Finally, claims 49-59 recite compositions comprising a polypeptide or oligomer of the claims discussed above as corresponding to the count, and a physiologically acceptable carrier, diluent or excipient. The TNF ligand family member molecules were expected to have therapeutic or diagnostic uses. Smith *et al.*, *Cell 76*:959-962 (1994) (Appendix L). Thus, it would have been obvious to formulate TNF ligand family member polypeptides, such as TRAIL, as pharmaceutical compositions comprising a physiological carrier, diluent, or excipient. Claims 49-59, accordingly, are the same patentable invention as Ruben Proposed Count A and should be designated as corresponding thereto. Accordingly, claims

1-26, 30-37, 40-43, and 45-59 should be designated as corresponding to Ruben Proposed Count A.

Table 1, a claim chart comparing claims 1-26, 30-37, 39-43, and 45-59 of the '236 patent to Ruben Proposed Count A, demonstrates how each of these claims corresponds to the proposed count as required under 37 C.F.R. § 41.202(a)(2):

Table 1: Wiley Claims That Correspond to Ruben Proposed Count A

'236 Patent Claim	**Limitation in Ruben Proposed Count A**
1. A purified tumor necrosis factor related apoptosis inducing ligand (TRAIL) polypeptide comprising an amino acid sequence that is at least 90% identical to an amino acid sequence selected from the group consisting of amino acids 1 to 281 of SEQ ID NO:2 and amino acids 1 to 291 of SEQ ID NO:6, wherein said TRAIL polypeptide induces apoptosis of Jurkat cells.	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising an amino acid sequence that is at least 90% identical to amino acids 1 to 281 of SEQ ID NO:2 ('236)
2. A purified TRAIL polypeptide comprising an amino acid sequence selected from the group consisting of amino acids 1 to 281 of SEQ ID NO:2 and amino acids 1 to 291 of SEQ ID NO:6.	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising amino acids 1 to 281 of SEQ ID NO:2.
3. A purified human TRAIL polypeptide encoded by the cDNA insert of the recombinant vector deposited in strain ATCC 69849.	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising amino acids 1 to 281 of SEQ ID NO:2, and this polypeptide is encoded by the cDNA insert of the recombinant vector deposited in strain ATCC 69849. Even if minor sequence differences were present in the cDNA insert of the recombinant vector deposited in strain ATCC 69849, *e.g.*, due to sequencing errors, Ruben Proposed Count A would still render Claim 3 obvious.
4. A purified soluble TRAIL polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence selected from the group consisting of: a) the extracellular domain of human TRAIL (amino acids 39 to 281 of SEQ ID NO:2); and b) a fragment of said extracellular domain; wherein said soluble TRAIL polypeptide induces apoptosis of Jurkat cells.	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising an amino acid sequence that is at least 90% identical to either: (a) amino acids 39 to 281 of SEQ ID NO:2 or (b) a fragment of said amino acid sequence wherein said polypeptide induces apoptosis. Alternatively, Ruben Proposed Count A renders this claim obvious because one of

	ordinary skill in the art would have easily been able to identify the extracellular domain, and active fragments and variants thereof, based on the known structure/function relationship of the TNF ligand family (*see* Appendix D), and would have been motivated to do so based on the known need for a soluble polypeptide.
5. A TRAIL polypeptide of claim 4, comprising an amino acid sequence selected from the group consisting of: a) the extracellular domain of human TRAIL (amino acids 39 to 281 of SEQ ID NO:2); and b) a fragment of said extracellular domain, wherein said fragment induces apoptosis of Jurkat cells.	This claim is anticipated or rendered obvious over Ruben Proposed Count A, because of the reasons stated for claim 4.
6. A purified TRAIL polypeptide comprising the sequence of amino acids x to 281 of SEQ ID NO:2, wherein x represents an integer from 39 to 95.	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising amino acids x to 281 of SEQ ID NO:2, wherein x represents an integer from 39 to 95. Alternatively, Ruben Proposed Count A renders this claim obvious because one of ordinary skill in the art would have easily been able to identify fragments of SEQ ID NO:2, based on the known structure/function relationship of the TNF ligand family (*see* Appendix D and M), and would have been motivated to do so based on the known need for a soluble polypeptide.
7. A TRAIL polypeptide of claim 6, comprising amino acids 95 to 281 of SEQ ID NO:2.	This claim is anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claim 6.

8. A TRAIL polypeptide of claim 4, wherein said soluble TRAIL polypeptide comprises conservative substitution(s) in an amino acid sequence selected from the group consisting of: a) the extracellular domain of human TRAIL (amino acids 39 to 281 of SEQ ID NO:2); and b) a fragment of said extracellular domain; wherein the conservatively substituted TRAIL induces apoptosis of Jurkat cells.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated in claim 4.
9. A purified TRAIL polypeptide, wherein said polypeptide is a fragment of the human TRAIL protein of SEQ ID NO:2, wherein said fragment induces apoptosis of Jurkat cells.	This claim is anticipated by Ruben Proposed Count A because Ruben Proposed Count A explicitly recites a fragment of amino acids 1 to 281 of SEQ ID NO:2, which induces apoptosis.
10. A TRAIL polypeptide of claim 9, wherein said fragment is a soluble polypeptide.	This claim is anticipated by Ruben Proposed Count A for the reasons stated for claim 9. Alternatively, Ruben Proposed Count A renders claim 10 obvious because one skilled in the art could routinely identify a soluble fragment of SEQ ID NO:2, based on the known structure/function relationship of the TNF ligand family (*see* Appendix D), and would have been motivated to do so based on the known need for a soluble polypeptide.
11. A fusion protein comprising a leucine zipper peptide and a soluble TRAIL polypeptide of claim 4, wherein said leucine zipper peptide is selected from the group consisting of the peptide of SEQ ID NO:14, a peptide consisting of amino acids 1 to 34 of SEQ ID NO:15, a peptide consisting of amino acids 2 to 34 of SEQ ID NO:15, a peptide consisting of amino acids 3 to 34 of SEQ ID NO:15, the peptide of SEQ ID NO:16, and the peptide of SEQ ID NO:17.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 4, and because one of ordinary skill in the art, having knowledge of the function of leucine zipper fusion proteins, *e.g.*, from PCT publication WO94/10308, would have been motivated to make a fusion protein comprising a leucine zipper fused to a polypeptide meeting the limitations claim 4, and would have had a reasonable expectation of success in making such a construct.
12. A fusion protein comprising a leucine zipper peptide and a soluble TRAIL polypeptide of claim 5, wherein said leucine zipper peptide is selected from the group consisting of the peptide of SEQ ID NO:14, a peptide consisting of amino acids 1 to 34 of SEQ ID NO:15, a peptide consisting of amino acids 2 to 34 of SEQ ID NO:15, a peptide consisting of amino acids 3 to 34 of SEQ ID NO:15, the peptide of SEQ ID NO:16, and the peptide of SEQ ID NO:17.	This claim is rendered obvious by Ruben Proposed Count A, for the reasons stated for claim 5 and because one of ordinary skill in the art, having knowledge of the function of leucine zipper fusion proteins, *e.g.*, from PCT publication WO94/10308, would have been motivated make a fusion protein comprising a leucine zipper fused to a polypeptide meeting the limitations of claim 5, and would have had a reasonable expectation of success in making such a construct.

13. A fusion protein comprising a leucine zipper peptide and a soluble TRAIL polypeptide of claim 6, wherein said leucine zipper peptide is selected from the group consisting of the peptide of SEQ ID NO:14, a peptide consisting of amino acids 1 to 34 of SEQ ID NO:15, a peptide consisting of amino acids 2 to 34 of SEQ ID NO:15, a peptide consisting of amino acids 3 to 34 of SEQ ID NO:15, the peptide of SEQ ID NO:16, and the peptide of SEQ ID NO:17.	This claim is rendered obvious by Ruben Proposed Count A, because of the reasons stated for claim 6, and because one of ordinary skill in the art, having knowledge of the function of leucine zipper fusion proteins, *e.g.*, from PCT publication WO94/10308, would have been motivated to make a fusion protein comprising a leucine zipper fused to a polypeptide meeting the limitations of claim 6, and would have had a reasonable expectation of success in making such a construct.
14. A fusion protein of claim 13, wherein said TRAIL polypeptide consists of amino acids 95 to 281 of SEQ ID NO:2.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 7 and 13
15. A fusion protein of claim 13, wherein said leucine zipper is a peptide consisting of amino acids 1 to 34 of SEQ ID NO:15.	This claim is rendered obvious by Ruben Proposed Count A because of the reasons stated for claim 13, and one of ordinary skill in the art would have been motivated to make a fusion protein where amino acids 1 to 34 of SEQ ID NO:15, disclosed in PCT publication WO94/10308, were fused to a polypeptide meeting the limitations of claim 13, and would have had a reasonable expectation of success in making such a construct.
16. A fusion protein of claim 11, additionally comprising the growth hormone leader of SEQ ID NO:19 at the N-terminus of said fusion protein.	This claim is rendered obvious by Ruben Proposed Count A because of the reasons stated for claim 11. In addition, one of ordinary skill in the art, would have been motivated to engineer such a fusion protein to be secreted, and the leader sequence for human growth hormone (SEQ ID NO:19) has been well known in the art since 1979 (*see Science 205*:602-607 (1979) (Appendix N).
17. A fusion protein of claim 16, wherein said leucine zipper is a peptide consisting of amino acids 1 to 34 of SEQ ID NO:15, wherein said TRAIL polypeptide consists of amino acids 95 to 281 of SEQ ID NO:2.	This claim is rendered obvious by Ruben Proposed Count A because of the reasons stated for claim 16. In addition, one of ordinary skill in the art, having knowledge of the function of leucine zipper fusion proteins, would have been motivated to make a fusion protein in which amino acids 1-34 of SEQ ID NO:15, disclosed in PCT publication WO94/10308, were fused to a fragment meeting the limitations of claim 16, and would have a reasonable expectation of success.
18. The fusion protein of claim 16, wherein said fusion protein comprises the amino acid sequence presented in SEQ ID NO:11.	This claim is rendered obvious by Ruben Proposed Count A, because of the reasons stated for claims 7 and 16. In addition, the skilled artisan would have been motivated, by

	necessity, to have tripeptide linkers between the various parts of the fusion protein because of the requirements of vector construction. In addition, a fragment of amino acids 1 to 281 of SEQ ID NO:2, as recited in Ruben Proposed Count A, is identical to a portion of the amino acid sequence presented in SEQ ID NO:11.
19. A fusion protein of claim 11, additionally comprising a CMV leader, comprising amino acids 1 to 29 of SEQ ID NO:9, at the N-terminus of said fusion protein.	This claim is rendered obvious by Ruben Proposed Count A because of the reasons stated for claim 11. Furthermore, one of ordinary skill in the art would have been motivated to engineer such a fusion protein to be secreted, and the CMV leader sequence, *i.e.*, amino acids 1 to 29 of SEQ ID NO:9, was well known in the art.
20. The fusion protein of claim 19, wherein said fusion protein comprises the amino acid sequence presented in SEQ ID NO:13.	This claim is rendered obvious by Ruben Proposed Count A, because of the reasons stated for claims 7 and 19. In addition, a fragment of amino acids 1 to 281 of SEQ ID NO:2, as recited in Ruben Proposed Count A, is identical to a portion of the amino acid sequence presented in SEQ ID NO:13.
21. A protein expressed by CHO cells transformed with an expression vector comprising the nucleotide sequence presented in SEQ ID NO:10.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 18, and because it would have been routine for the skilled artisan to transform CHO cells with an expression vector.
22. A protein expressed by CHO cells transformed with an expression vector comprising the nucleotide sequence presented in SEQ ID NO:12.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 20, and because it would have been routine for the skilled artisan to transform CHO cells with an expression vector.
23. A purified oligomer comprising at least two soluble TRAIL polypeptides of claim 4.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claim 4, and because it was well known that TNF ligand family proteins exist in soluble oligomeric forms *in vivo* (*see* Appendix G), so one of ordinary skill in the art would have been motivated to produce oligomeric forms of the fragments recited in Ruben Proposed Count A. It was also known how to make soluble oligomeric forms, and therefore one skilled in the art would have had a reasonable expectation of success preparing oligomeric forms of the fragments recited in Ruben Proposed Count A.
24. A purified oligomer comprising two or three soluble TRAIL polypeptides of claim 5.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count

	A for the reasons stated for claims 5 and 23..
25. A purified oligomer comprising two or three soluble TRAIL polypeptides of claim 6.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claims 6 and 23.
26. An oligomer comprising at least two fusion proteins of claim 11.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claims 11 and 23.
30. A purified TRAIL protein, wherein said protein is expressed by E. coli cells transformed with an expression vector comprising a nucleotide sequence selected from the group consisting of: a) nucleotides 88 to 933 of the sequence presented as SEQ ID NO:1; b) nucleotides 47 to 922 of the sequence presented as SEQ ID NO:5; c) a fragment of the nucleotide sequence of (a); d) a fragment of the nucleotide sequence of (b); and e) a nucleotide sequence that is degenerate as a result of the genetic code to a sequence of (a), (b), (c), or (d); wherein said protein induces apoptosis of TRAIL-sensitive cancer cells.	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide or active fragment thereof encoded by a nucleotide sequence comprising the nucleotides recited in Claim 30(a) or (c)-(e). Alternatively, this claim is rendered obvious by Ruben Proposed Count A, because it would have been routine for the skilled artisan to produce an isolated polypeptide of Ruben Proposed Count A, which is encoded by a polynucleotide recited in Claim 30(a) or (c)-(e), by way of an *E. coli* expression vector, and one would have had a reasonable expectation of success. Furthermore, at least one fragment of amino acids 1 to 281 of SEQ ID NO:2 that has apoptosis inducing activity is a fragment of "the nucleotide sequence of (a)," and induces apoptosis of TRAIL-sensitive cells for the reasons stated for claim 4.
31. A protein of claim 30, wherein said nucleotide sequence additionally encodes a methionine residue at the N-terminus of said protein.	This claim is anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claim 30, and because nucleotides 88 to 90 of SEQ ID NO:1 ('236) codes for methionine. Furthermore, one of ordinary skill in the art would have been motivated to ensure that the polypeptide includes a N-terminal methionine added to the nucleotide sequence encoding a fragment of amino acids 1 to 281 of SEQ ID NO:2 to allow expression given that AUG (which codes for methionine) is the start codon for protein expression.
32. A TRAIL protein of claim 30, wherein said protein is in the form of an oligomer.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claims 30 and 23.
33. A purified polypeptide comprising amino acids 124 to 276 of SEQ ID NO:2.	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising amino acids 124 to 276 of SEQ ID NO:2 ('236).

34. A purified polypeptide, wherein said polypeptide is a soluble fragment of the TRAIL protein of SEQ ID NO:2, wherein the N-terminal amino acid of said fragment is selected from residues 39 to 124 of SEQ ID NO:2, and the C-terminal amino acid of said fragment is selected from residues 276 to 281 of SEQ ID NO:2.	Ruben Proposed Count A renders this claim obvious because one of ordinary skill in the art would have easily been able to identify fragments of SEQ ID NO:2, based on the known structure/function relationship of the TNF ligand family (*see* Appendix D), and would have been motivated to do so based on the known need for a soluble polypeptide.
35. A purified polypeptide comprising a fragment of the protein of SEQ ID NO:2, wherein said fragment kills TRAIL-sensitive target cells.	This claim is anticipated by Ruben Proposed Count A for the reasons stated for claim 9.
36. A purified TRAIL polypeptide comprising the amino acid sequence presented in SEQ ID NO:2 or SEQ ID NO:6, with the proviso that said polypeptide lacks a transmembrane region, wherein said polypeptide is capable of killing TRAIL-sensitive target cells.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 4.
37. A purified oligomer comprising two or more polypeptides of claim 7.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claims 7 and 23.
39. A purified oligomer comprising two or more polypeptides of claim 33.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claims 33 and 23.
40. A purified oligomer comprising two or more polypeptides of claim 34.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claims 34 and 23.
41. A purified oligomer comprising two or more polypeptides of claim 35.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claims 34 and 23.
42. A purified oligomer comprising two or more TRAIL polypeptides, wherein each of said TRAIL polypeptides is a fragment of the protein of SEQ ID NO:2, wherein said oligomer kills TRAIL-sensitive target cells.	This claim is inherently anticipated or rendered obvious by Ruben Proposed Count A for the reasons stated for claims 9 and 23.
43. An oligomer of claim 37, wherein said oligomer contains three of said polypeptides.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 37.
45. An oligomer of claim 39, wherein said oligomer contains three of said polypeptides.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 39.
46. An oligomer of claim 40, wherein said oligomer contains three of said polypeptides.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 40.

47. An oligomer of claim 41, wherein said oligomer contains three of said polypeptides.	This claim is rendered obvious by Ruben Proposed Count A for the reason stated for claim 41.
48. An oligomer of claim 42, wherein said oligomer contains three of said polypeptides.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 42.
49. A composition comprising a polypeptide of claim 1, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 1, and because one of ordinary skill in the art would have been motivated to make such a composition because TNF ligand family member molecules were expected in the art to have therapeutic and diagnostic uses.
50. A composition comprising a polypeptide of claim 5, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 5 and 49.
51. A composition comprising an oligomer of claim 23, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 23 and 49.
52. A composition comprising an oligomer of claim 24, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 24 and 49.
53. A composition comprising a protein of claim 32, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 32 and 49.
54. A composition comprising an oligomer of claim 37, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 37 and 49.
55. A composition comprising an oligomer of claim 40, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 40 and 49.
56. A composition comprising an oligomer of claim 41, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 41 and 49.
57. A composition comprising an oligomer of claim 42, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 42 and 49.
58. A composition comprising an oligomer of claim 48, and a physiologically acceptable carrier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 48 and 49.
59. A composition comprising an oligomer of claim 45, and a physiologically acceptable canier, diluent, or excipient.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 45 and 49.

For the foregoing reasons, claims 1-26, 30-37, 39-43, and 45-59 of the Wiley '236 patent are directed to the same patentable invention as RUBEN PROPOSED COUNT A and should be designated as corresponding to that count.

2. Ruben Claims Which Correspond to Ruben Proposed Count A

Ruben's pending claims 8-10, 12-15, 17, 25, 27 and 30-38 are drawn to a purified protein which comprises amino acids 1 to 281 of SEQ ID NO:2 ('429), a purified protein which comprises amino acids 39-281 of SEQ ID NO:2 ('429), a purified protein encoded by a cDNA clone from which the nucleotide sequence encoding amino acids 1 to 281 of SEQ ID NO:2 ('429) was derived, purified proteins consisting of at least 30 or 50 contiguous amino acids of SEQ ID NO:2, a purified protein consisting of a polypeptide sequence that is a fragment of amino acids 1 to 281 of SEQ ID NO:2, wherein said polypeptide sequence has a biological activity selected from the group consisting of (a) producing an antibody specific to the polypeptide of SEQ ID NO:2; (b) inducing apoptosis of a cell line derived from pathologic tissue; and (c) inducing apoptosis of T cells, a purified protein produced by a process comprising: expressing in a host cell a nucleic acid encoding said protein so as to produce said protein, wherein the nucleic acid is selected from the group consisting of (a) a polynucleotide encoding amino acids 1 to 281 of SEQ ID NO:2;(b) a polynucleotide encoding amino acids 39 to 281 of SEQ ID NO:2; and (c) a polynucleotide encoding the amino acid sequence encoded by the human cDNA contained in ATCC Deposit No. 97448, fusion proteins comprising these claimed proteins, and compositions comprising these claimed proteins. As indicated above, SEQ ID NO:2 ('429) and SEQ ID NO:2 ('236) share an identical amino acid sequence, i.e. they are the same protein.

Claims 8-10 relate to AIM-I fragments, which are identical to a fragment of amino acids 1 to 281 of SEQ ID NO:2 recited in Ruben Proposed Count A, and, as such, are the same patentable invention.

Claims 13-15 are drawn to polypeptides comprising the full-length AIM-I protein and the extracellular domain fragment. Ruben Proposed Count A would anticipate or render obvious such polypeptides, and, as such, is the same patentable invention. Ruben Proposed Count A anticipates claims 13 and 14 because Ruben Proposed Count A recites a polypeptide comprising amino acids 1 to 281 of SEQ ID NO:2 encoded by the human cDNA contained in ATCC Deposit No. 97448. Ruben Proposed Count A anticipates claim 15 because Ruben Proposed Count A also recites a polypeptide comprising the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448. Alternatively, Ruben Proposed Count A renders claim 15 obvious because one of ordinary skill in the art would have easily been able to identify the mature form based on the known structure/function relationship of the TNF ligand family (*see* Appendix D), and would have been motivated to do so based on the known need for a mature polypeptide. Even if minor sequencing differences were present in the human cDNA contained in ATCC Deposit No. 97448, *e.g.*, due to sequencing errors, Ruben Proposed Count A would still render claims 13-15 obvious.

Claims 25 and 37 recite the AIM-I protein and the extracellular domain of AIM-I that have been recombinantly produced in a host cell. Recombinant production of proteins is elementary to biotechnology and in no way constitutes a patentable distinction. *See* Appendix I.

Claims 30-32 are drawn to a purified protein which comprises amino acids 1 to 281 of SEQ ID NO:2 ('429), or a purified protein which comprises amino acids 39-281 of SEQ ID NO:2 ('429). Ruben Proposed Count A anticipates or alternatively, renders obvious the polypeptides of claims 30-32, and, as such, is the same patentable invention.

Claims 34 and 35 recite fusion proteins, and claims 12, 17, 27, 33, 36, and 38 recite compositions comprising a polypeptide of the claims discussed above as corresponding to the

count, and a physiologically acceptable carrier. As indicated above, it would have been obvious to use TNF ligand family member polypeptides, such as SEQ ID NO:2 ('429), in fusion constructs or in pharmaceutical or diagnostic compositions. Claims 12, 17, 27, 33-36 and 38, accordingly, are the same patentable invention as the proposed Count A and should be designated as corresponding thereto.

Table 2, a claim chart comparing claims 8-10, 12-15, 17, 25, 27 and 30-38 of the present application to Ruben Proposed Count A demonstrates how each of these claims corresponds to the proposed count as required under 37 C.F.R. § 41.202(a)(2):

Table 2: Ruben Claims That Correspond to Ruben Proposed Count A

'429 Application Claim	**Limitation in Ruben Proposed Count A**
8. A purified protein consisting of at least 30 contiguous amino acids of SEQ ID NO:2.	This claim is anticipated by Ruben Proposed Count A, because amino acids 1 to 281 of SEQ ID NO:2 ('429), as recited in Ruben Proposed Count A, consists of at least 30 contiguous amino acids of SEQ ID NO:2.
9. The purified protein of claim 8 consisting of at least 50 contiguous amino acids of SEQ ID NO:2.	This claim is anticipated by Ruben Proposed Count A, because amino acids 1 to 281 of SEQ ID NO:2 ('429), as recited in Ruben Proposed Count A, consists of at least 50 contiguous amino acids of SEQ ID NO:2.
10. A purified protein consisting of a polypeptide sequence that is a fragment of amino acids 1 to 281 of SEQ ID NO:2, wherein said polypeptide sequence has a biological activity selected from the group consisting of: (a) producing an antibody specific to the polypeptide of SEQ ID NO:2; (b) inducing apoptosis of a cell line derived from pathologic tissue; and (c) inducing apoptosis of T cells.	This claim is anticipated by Ruben Proposed Count A because Ruben Proposed Count A explicitly recites a fragment of amino acids 1 to 281 of SEQ ID NO:2, which induces apoptosis.
12. A composition comprising the purified protein of claim 10 and a pharmaceutically acceptable carrier.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 10, and because one of ordinary skill in the art would have been motivated to make such a composition, because TNF ligand family member molecules were known in the art to have potential therapeutic and diagnostic uses.

13. A purified protein comprising a polypeptide sequence selected from the group consisting of: (a) the amino acid sequence of the full-length polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448; and (b) the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448.	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising amino acids 1 to 281 of SEQ ID NO:2, and this polypeptide is encoded by the human cDNA contained in ATCC Deposit No. 97448. Even if minor sequence differences were present in the human cDNA contained in ATCC Deposit No. 97448, *e.g.*, due to sequencing errors, Ruben Proposed Count A would still render Claim 15 obvious.
14. The purified protein of claim 13, wherein said polypeptide sequence is (a).	This claim is anticipated or rendered obvious by Ruben Proposed Count A, for the reasons stated for claim 13.
15. The purified protein of claim 13, wherein said polypeptide sequence is (b).	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising the amino acid sequence of the mature polypeptide encoded by the human cDNA contained in ATCC Deposit No. 97448. Alternatively, Ruben Proposed Count A renders this claim obvious because one of ordinary skill in the art would have easily been able to identify the mature form based on the known structure/function relationship of the TNF ligand family (*see* Appendix D), and would have been motivated to do so based on the known need for a mature polypeptide. Moreover, even if minor sequence differences were present in the human cDNA contained in ATCC Deposit No. 97448, *e.g.*, due to sequencing errors, Ruben Proposed Count A would still render Claim 15 obvious.
17. A composition comprising the purified protein of claim 13 and a pharmaceutically acceptable carrier.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 12 and 13.
25. A purified protein produced by a process comprising: expressing in a host cell a nucleic acid encoding said protein so as to produce said protein, wherein the nucleic acid is selected from the group consisting of: (a) a polynucleotide encoding amino acids 1 to 281 of SEQ ID NO:2; (b) a polynucleotide encoding amino acids 39 to 281 of SEQ ID NO:	This claim is rendered obvious by Ruben Proposed Count A, because it would have been routine for the skilled artisan to produce a purified polypeptide or polypeptide fragment of Ruben Proposed Count A by way of expressing a nucleic acid encoding said protein in a host, and such expression would have had a reasonable expectation of success.

2; and (c) a polynucleotide encoding the amino acid sequence encoded by the human cDNA contained in ATCC Deposit No. 97448.	
27. A composition comprising the purified protein of claim 25 and a pharmaceutically acceptable carrier.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 12 and 25..
30. A purified protein comprising a polypeptide selected from the group consisting of: (a) amino acids 1 to 281 of SEQ ID NO:2; and (b) amino acids 39 to 281 of SEQ ID NO:2.	This claim is anticipated by Ruben Proposed Count A because Ruben Proposed Count A explicitly recites a polypeptide comprising amino acids 1 to 281 of SEQ ID NO:2.
31. The purified protein of claim 30, wherein said polypeptide, sequence is (a).	This claim is anticipated by Ruben Proposed Count A for the reasons stated for claim 30.
32. The purified protein of claim 30, wherein said polypeptide sequence is (b).	This claim is anticipated by Ruben Proposed Count A, because Ruben Proposed Count A recites a polypeptide comprising the amino acids 39 to 281. Alternatively, Ruben Proposed Count A renders this claim obvious because one of ordinary skill in the art would have easily been able to identify the mature form based on the known structure/function relationship of the TNF ligand family (*see* Appendix D), and would have been motivated to do so based on the known need for a mature polypeptide.
33. A composition comprising the purified protein of claim 30 and a pharmaceutically acceptable carrier.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 12 and 30.
34. A purified protein consisting of at least 30 contiguous amino acids of SEQ ID NO:2, fused to a heterologous polypeptide.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 8, and because one of ordinary skill in the art would have been motivated to fuse heterologous polypeptides to the isolated polypeptide and polypeptide fragment of Ruben Proposed Count A, *e.g.*, to allow for protein secretion or to increase protein stability, and would have a reasonable expectation of success in making such a construct.
35. The protein of claim 34, wherein said protein consists of at least 50 contiguous amino acids of SEQ ID NO:2, fused to a heterologous polypeptide.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 9 and 34.

36. A composition comprising the purified protein of claim 34 and a pharmaceutically acceptable carrier.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 12 and 34.
37. The protein of claim 25, wherein said host cell is a eukaryotic cell.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claim 25, and because it would have been routine for the skilled artisan to produce an isolated polypeptide or polypeptide fragment of Ruben Proposed Count A by way of expressing a nucleic acid encoding said protein in an eukaryotic host (*see, e.g.*, Gluzman *et al.*, *Cell 23*:175 (1981) (Appendix O)) and such expression would have had a reasonable expectation of success.
38. A composition comprising the purified protein of claim 8 and a pharmaceutically acceptable carrier.	This claim is rendered obvious by Ruben Proposed Count A for the reasons stated for claims 12 and 8.

For the foregoing reasons, claims 8-10, 12-15, 17, 25, 27 and 30-38 of the Ruben '429 application are directed to the same patentable invention as RUBEN PROPOSED COUNT A and should be designated as corresponding to that count.

C. Demonstration of Interfering Subject Matter as Required under 37 C.F.R. § 41.202(a)(3)

Claims are drawn to interfering subject matter "if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party, and vice versa. 37 C.F.R. § 41.203(a). Table 3 is a claim chart comparing claim 30 of the present application to claim 2 of the '236 patent.

TABLE 3

Ruben '429 Application Claim 30	**Wiley '236 Patent Claim 2**
30. A purified protein comprising a polypeptide selected from the group consisting of:	2. A purified TRAIL polypeptide comprising an amino acid sequence selected from the group consisting of:
amino acids 1 to 281 of SEQ ID NO:2; and	amino acids 1 to 281 of SEQ ID NO:2 and
amino acids 39 to 281 of SEQ ID NO:2.	amino acids 1 to 291 of SEQ ID NO:6.

Claim 30 of the present application, if prior art, would anticipate claim 2 of the '236 patent. Amino acids 1 to 281 of SEQ ID NO:2 ('429) is identical to amino acids 1 to 281 of SEQ ID NO:2 ('236). Since a polypeptide recited in claim 30 of the '429 application is identical to a polypeptide recited in the Markush group of claim 2 of the '236 patent, claim 30 of the '429 patent, if prior art, would anticipate claim 2 of the '236 patent.

Similarly, claim 2 of the '236 patent, if prior art, would anticipate claim 30 of the '429 application. Amino acids 1 to 281 of SEQ ID NO:2 ('236) is identical to amino acids 1 to 281 of SEQ ID NO:2 ('429). Since a polypeptide recited in claim 2 of the '236 patent is identical to a polypeptide recited in the Markush group of claim 30 of the '429 application, claim 2 of the '236 patent, if prior art, would anticipate claim 30 of the '429 application.

For the foregoing reasons, at least one claim of the Ruben '429 application and at least one claim of the '236 patent recite interfering subject matter as required under 37 C.F.R. § 41.203(a)(3).

D. 37 C.F.R. § 41.202(a)(4)

A detailed analysis of why the Applicant will prevail on priority is found in the accompanying *PRIMA FACIE* SHOWING OF ENTITLEMENT TO JUDGMENT Pursuant to 37 C.F.R. § 41.202(d).

E. 37 C.F.R. § 41.202(a)(5)

Table 4 is a claim chart showing that the present claims of the '429 application do not differ from the earlier claims of the '405 and '981 applications in any material limitation.

TABLE 4

Ruben '405 and '981 Applications Claim 13	**Ruben '429 Application Claim 30**
13. A polypeptide comprising a member selected from the group consisting of:	30. A purified protein comprising a polypeptide selected from the group consisting of:
(a) a polypeptide having an amino acid sequence set forth in SEQ ID NO:2; and	(a) amino acids 1 to 281 of SEQ ID NO:2;
(b) a polypeptide which is at least 70%	(b) amino acids 39 to 281 of SEQ ID

identical to the polypeptide of (a).	NO:2
Claim 14	**Claim 31**
14. The polypeptide of Claim 13 wherein the polypeptide comprises	31. The purified protein of claim 30
amino acid 1 to amino acid 281 of SEQ ID NO:2.	wherein said polypeptide sequence is (a).

Claim 14 of the '405 and '981 applications recites a polypeptide comprising amino acid 1 to 281 of SEQ ID NO:2. This claim is substantively identical to claim 31 of the present '430 application which recites a purified protein comprising a polypeptide sequence of amino acids 1 to 281 of SEQ ID NO:2. SEQ ID NO:2 of the '404, '981, and '429 applications are identical.

Accordingly, substantially similar subject matter to all of Applicant's claims 8-10, 12-15, 17, 25, 27 and 30-38 was previously pending in the immediate parent of the '429 application. Accordingly, no showing is required under Rule 202(a)(5) with respect to those claims.

F. 37 C.F.R. § 41.202(a)(6)

Disclosure demonstrating constructive reduction to practice for each limitation recited in Ruben's Proposed Count A is found in Table 5.

TABLE 5

Ruben's Proposed Count A	**Support in Disclosure of '405 Application (Attached as Appendix P)**
An isolated polypeptide comprising	Page 25
amino acids 1 to 281 of SEQ ID NO:2 or	Page 28
a fragment thereof, wherein said fragment has apoptosis inducing activity.	Page 28, page 44

Applicant's captioned '429 application is a divisional of Application No. 08/816,981, filed March 13, 1997 which claims the benefit under 35 U.S.C. § 119(e) of provisional Application No. 60/013,405 filed March 14, 1996. Since both of Applicant's priority

applications have the identical specification as the '429 application, Applicant is entitled to the benefit of the filing date of the priority application for RUBEN PROPOSED COUNT A.

III. CONCLUSION

Applicant respectfully requests that an interference be declared between the captioned '429 application and the Wiley '236 patent over the subject matter of RUBEN PROPOSED COUNT A, and that claims 8-10, 12-15, 17, 25, 27, and 30-38 of the '429 application and claims 1-26, 30-37, 39-43, and 45-59 of the Wiley '236 patent be designated as corresponding to that count. Applicant is entitled to the benefit of the filing date of the priority application for RUBEN PROPOSED COUNT A.

Respectfully submitted,

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Attachments:

Appendix A:	RUBEN PROPOSED COUNT A
Appendix B:	Wiley *et al.*, Patent No. 6,284,236 issued September 4, 2001 ("the '236 patent")
Appendix C	Pakula, AA and Sauer, RT, *Annual Review of Genetics 23*:289-310 (1989)
Appendix D	Gruss and Dower, *Blood 85*:3378-3404 (1995)
Appendix E	Landschulz *et al.*, *Science 240*:1759 (1988)
Appendix F	PCT Publication WO 94/10308, entitled "Method of Preparing Soluble Oligomeric Proteins," published May 11, 1994

Appendix G	Beutler *et al., Science 264*:667-668 (1994)
Appendix H	Engelmann *et al., J. Biol. Chem. 265*:14497-14504 (1990)
Appendix I	Watson *et al.*, Recombinant DNA: A Short Course. 96-97 W.H. Freeman & Co. (1983)
Appendix J	Ausubel *et al.*, Current Protocols in Molecular Biology 16 (1994)
Appendix K	Pecceu *et al.*, *Gene 97*:253-258 (1991)
Appendix L	Smith *et al.*, *Cell 76*:959-962 (1994)
Appendix M	Fanslow *et al.*, *Semin. Immunol. 6*:267-278 (1994)
Appendix N	Martial *et al.*, *Science 205*:602-607 (1979)
Appendix O	Gluzman *et al.*, *Cell 23*:175 (1981)
Appendix P	U.S. Provisional Patent Application 60/013,405

APPENDIX A

RUBEN PROPOSED COUNT A

An isolated polypeptide comprising amino acids 1 to 281 of SEQ ID NO:2 or a fragment thereof, wherein said fragment has apoptosis inducing activity.